Tenofovir Disoproxil Fumarate (TDF, Viread)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablet: 300 mg

Combination tablets:

- *With emtricitabine (FTC):* TDF 300 mg + FTC 200 mg (Truvada)
- With FTC + efavirenz *(EFV):* TDF 300 mg + FTC 200 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:
TDF is not approved for use in neonates/infants.

Pediatric dose*:
TDF is not approved for use in children <12 years of age. Investigational doses of 210 mg/m^2 body surface area (range 175 to 300 mg/m^2) have been used once daily in children <12 years of age.

Adolescent (≥12 years of age and body weight >35 kg) dose*:
300 mg once daily
*See Pediatric Use for concerns about decreased bone mineral density (BMD), especially in prepubertal patients and those in early puberty (Tanner Stages 1 and 2).

Combination Tablets
Adult dose: 300 mg once daily.

Truvada (TDF + FTC)
Adult dose: 1 tablet once daily.

Atripla (TDF + FTC + EFV)
Adult dose: 1 tablet once daily.

TDF in combination with didanosine (ddI):
The combination of TDF and ddI should be avoided if possible. If used, ddI dose requires modification. See section on ddI.

TDF in combination with atazanavir (ATV):
When ATV is used in combination with TDF, ATV should always be boosted with ritonavir (RTV).

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased BMD

Special Instructions

- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains EFV, the combination tablet should be administered on an empty stomach.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV can occur when TDF is discontinued; therefore, monitor hepatic function for several months after therapy with TDF is stopped.

Metabolism

- Renal excretion.
- **Dosing of ddI in patients with renal insufficiency:** Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).
  - Atripla (fixed-dose combination) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
  - Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is coadministered with tenofovir and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors (PIs):* Tenofovir decreases atazanavir plasma concentrations. In adults, the recommended dosing for atazanavir coadministered with tenofovir is atazanavir 300 mg with ritonavir 100 mg and tenofovir 300 mg, all as a single daily dose with food. Atazanavir without ritonavir should not be coadministered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.

Major Toxicities:

- *More common:* Nausea, diarrhea, vomiting, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen (BUN), glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TDF.html).

Pediatric Use: Tenofovir is Food and Drug Administration (FDA) approved for use in children ≥12 years of age and ≥35 kg body weight when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (Tanner Stages 1 and 2) appear to be at higher risk than children with more advanced development (Tanner Stage ≥3)[1-3]. In a Phase I/II National Institutes of Health (NIH) study of an investigational 75-mg formulation of tenofovir involving 18 heavily pretreated children and adolescents, a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DXA) scan was reported in 5 of 15 (33%) children evaluated at Week 48[1]. Two of the 5 children who discontinued tenofovir at 48 weeks experienced partial or complete recovery of BMD by 96 weeks[4]. Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years[4-5]. In a second study of 6 patients who received the commercially available 300-mg formulation of tenofovir, 2 prepubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her antiretroviral therapy (ART) regimen with subsequent recovery of BMD[6]. Loss of BMD at 48 weeks was associated with higher drug exposure (area under the curve [AUC])[5]. Factors contributing to higher drug exposure in these studies included receiving ritonavir,

which increases tenofovir concentrations, and receiving higher doses of tenofovir. Although the median initial dose in the Phase I/II studies was 208 mg/m^2 (= 7.1 mg/kg), the administered dose varied from 161 to 256 mg/m^2 (3.7–10 mg/kg)[1]. However, in this heavily pretreated cohort, the group with the best virologic response had statistically significantly higher AUC, suggesting that in salvage therapy tenofovir may have a relatively small therapeutic window, especially in children in Tanner Stages 1 and 2. Plasma HIV RNA concentrations ($\log_{10}$ copies/mL) decreased from a median pretreatment concentration of 5.4 $\log_{10}$ copies/mL to 4.21 $\log_{10}$ copies/mL after 48 weeks of therapy[5]. HIV RNA was <400 copies/mL in 6 of 16 participants (37.5%) and <50 copies/mL in 4 of 16 participants (25%) at 48 weeks. In contrast, no effect of tenofovir on BMD was found in another study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz[7]. This study enrolled children who were older, not receiving ritonavir, and receiving lower doses of tenofovir with potentially lower drug exposures[7-9]. All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen. Lipid profiles improved significantly after the switch from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz[8].

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in persons with higher tenofovir trough plasma concentrations[10]. Renal toxicity leading to discontinuation of tenofovir was reported in 3.7% (6 of 159) of HIV-1-infected children treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland[11]. Possible tenofovir-associated nephrotoxicity manifest as Fanconi syndrome, reduced CrCl, and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including lopinavir/ritonavir and didanosine for 1 year[12]. Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine[13]. Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 27% (12 of 44) of children treated with tenofovir compared with 4% (2 of 48) of children not treated with tenofovir[14]. An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing cART[15]. Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovir-containing ARV regimens from 5 Spanish hospitals. The patients ranged in age from 8 to 17 years (median age 12.5 years) and had received tenofovir for 16 to 143 months (median 77 months). The following observations were made: 18 patients had declines in CrCl after at least 6 months of therapy; 28 patients had decreases in tubular reabsorption of phosphate, which worsened with longer time on tenofovir; and 33 patients had proteinuria, including 10 patients with proteinuria in the nephrotic range[16]. However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years[17].

Pharmacokinetic (PK) studies in children receiving an investigational 75-mg tablet formulation of tenofovir showed that a median dose of 208 mg/m^2 of body surface area (range 161–256 mg/m^2 body surface area) resulted in a median single dose AUC and maximum plasma concentration (C_{max}) that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg[1, 18]. Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure[1]. This lower exposure occurred even though participants were concurrently treated with ritonavir, which boosts tenofovir exposure. Lower than anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir[19].

Virologic success is related to prior treatment experience when evaluating the response to a tenofovir-containing regimen. In the CHIPS cohort 115 patients had outcome data available[11]. Viral load decreased

to <50 copies/mL at 12 months in 38% of patients starting tenofovir for the first time, in 50% of patients on first-line therapy, in 39% of patients on second-line therapy, and in 13% of patients on third-line or subsequent therapy[11]. The CHIPS cohort used a target dose of 8 mg/kg, but 18% of patients were dosed at greater than 120% of the target dose and 37% were dosed at less than 80% of the target dose.

Virologic success is also related to drug exposure. In the NIH study[5], lower single-dose and steady-state AUC were associated with inferior virologic outcome. The Italian study[8], which used a lower dose than the NIH study (and reported less bone toxicity), studied only subjects who were well controlled on current ART.

In March 2010, the FDA approved the use of tenofovir in adolescents ≥12 years of age and weighing ≥35 kg based upon data from Gilead Study 321, a randomized, placebo-controlled trial of tenofovir or placebo plus an optimized background regimen in 87 treatment-experienced adolescents 12 to <18 years of age in Brazil and Panama[20-21]. No difference in viral load response was seen between the 2 groups. Subgroup analyses suggest this lack of response may have been due to imbalances in viral susceptibility to the optimized background regimens between the 2 groups. Importantly, impaired bone accrual was seen in the tenofovir group, manifest by declining BMD *z* scores over 48 and 96 weeks. In addition, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with only 1 of 33 participants (3%) in the placebo arm[20-21] (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM209151.pdf). Limited PK data were reported from 8 participants and suggested that tenofovir exposures were higher than those seen in the NIH study, but no data on correlation of tenofovir exposure with BMD loss were provided.

Although some studies of tenofovir use in children have not identified decline in BMD[22-23], given the potential for BMD loss, some experts recommend obtaining a DXA prior to the initiation of tenofovir therapy and approximately 6 months after start of tenofovir, especially in prepubertal patients and those early in puberty (Tanner Stages 1 and 2). However, in view of the potential cost and difficulty in obtaining pediatric DXA in some settings, other experts avoid using tenofovir in prepubertal patients and those in early puberty, especially for initial therapy. Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in early adolescence is concerning and favors judicious use of tenofovir in this age group. There is still an urgent need for more research to develop appropriate pediatric formulations and to identify the safest uses of tenofovir in children and adolescents.

References

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